ROXANE LABORATORIES, INC.

ORLAAM® C II

Levomethadyl Acetate Hydrochloride Oral Solution

R_x only

Due to its potential for serious and possibly life-threatening, proarrhythmic effects, LAAM should be reserved for use in the treatment of opiate-addicted patients who fail to show an acceptable response to other adequate treatments for opiate addiction, either because of insufficient effectiveness or the inability to achieve effective dose due to intolerable adverse effects from those drugs (see Warnings and Contraindications).

Cases of QT prolongation and serious arrhythmia (torsade de pointes) have been observed during post-marketing treatment with ORLAAM. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of ORLAAM to determine if a prolonged QT interval (QTc greater than 430 [male] or 450 [female] ms) is present. If there is a prolonged QT interval, ORLAAM should NOT be administered. For patients in whom the potential benefit of ORLAAM treatment is felt to outweigh the risks of potentially serious arrhythmias, an ECG should be performed prior to treatment, 12-14 days after initiating treatment, and periodically thereafter, to rule out any alterations in the QT interval.

ORLAAM should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diurectic,cardiac hypertrophy, hypokalemia, or hypomagnesemia).

ORLAAM is metabolized to active metabolites by the cytochrome P450 isoform, CYP3A4. Therefore, the addition of drugs that induce this enzyme (such as rifampin, phenobarbital, and phenytoin) or inhibit this enzyme (such as ketoconazole, erythromycin, and saquinavir) could increase the levels of parent drug or its active metabolites in a patient that was previously at steady-state, and this could potentially precipitate serious arrhythmias, including torsade de pointes (see PRECAUTIONS, Drug Interactions).

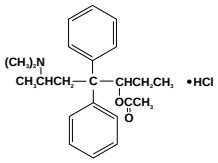
CONDITIONS FOR DISTRIBUTION AND USE OF ORLAAM (42 CFR Part 8)

ORLAAM, used for the treatment of opiate addiction, shall be dispensed only by Opioid Treatment Programs (OTPs) certified by SAMHSA under 42 CFR Part 8, and registered by the Drug Enforcement Administration under 21. U.S.C. 823(g)(1). This does not preclude the maintenance or detoxification treatment of a patient who is hopsitalized for medical conditions other than opiate addiction and who requires temporary maintenance for concurrent opiate addiction during the critical period of the patient's hospitalization. Failure to abide by these requirements may result in injunction precluding operation of the program, revocation of the program approval, and possible criminal prosecution.

ORLAAM has no recommended uses outside of the treatment of opiate addiction.

DESCRIPTION

ORLAAM (brand of levomethadyl acetate hydrochloride) is a synthetic opiate agonist. Chemically, it is levo-alpha-6-dimethylamino-4, 4-diphenyl-3-heptyl acetate hydrochloride, $C_{23}H_{31}NO_2 \cdot HCl$. It is also known as levo-alpha-acetylmethadol hydrochloride (LAAM). The structural formula is:



The compound is a white crystalline powder, soluble in water (>15 mg/mL), ethanol, and methyl ethyl ketone. The octanol:water partition coefficient of LAAM is 405:1 at physiologic pH. Doses of ORLAAM (LAAM) are always expressed as the weight of the hydrochloride salt (molecular weight 389.95).

ORLAAM is an aqueous solution which is diluted for oral administration. Each one mL of ORLAAM contains: Levomethadyl acetate hydrochloride (LAAM) 10 mg. Inactive ingredients: Methylparaben, propylparaben, hydrochloric acid and water.

CLINICAL PHARMACOLOGY

LAAM is a synthetic opioid agonist with actions qualitatively similar to morphine (a prototypic mu agonist) and affecting the central nervous system (CNS) and smooth muscle. Principal actions include analgesia and sedation. Tolerance to these effects develops with repeated use.

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An abstinence syndrome generally occurs upon cessation of chronic administration similar to that observed with other opiates, but with slower onset, more prolonged course, and less severe symptoms.

LAAM exerts its clinical effects in the treatment of opiate abuse through two mechanisms. First, LAAM cross-substitutes for opiates of the morphine-type, suppressing symptoms of withdrawal in opiate-dependent individuals. Second, chronic oral administration of LAAM can produce sufficient tolerance to block the subjective "high" of usual doses of parenterally administered opiates.

LAAM is metabolized by N-demethylation to nor-LAAM and dinor-LAAM, which are also opioid agonists. These metabolites are more potent than the parent drug. The opioid effect which occurs when LAAM is administered is slower in onset and longer in duration (72 hours) than that of methadone (24 hours). This extended duration of action allows three-times-weekly administration (see CLINICAL TRIALS).

PHARMACODYNAMICS

The duration of action of a single dose of LAAM is due to the sum of the opioid activity of the parent drug and its metabolites. A single dose of orally administered LAAM has an onset of opioid effects averaging 2 to 4 hours after ingestion and a duration of action of 48 to 72 hours (as measured by pupillary constriction and suppression of abstinence signs). LAAM cross-substitutes for opiates like morphine in opiate-dependent individuals, suppressing symptoms of withdrawal from these compounds. Single oral doses of 30 to 60 mg of LAAM eliminate signs of abstinence for 24 to 48 hours in individuals maintained on high doses of morphine who are abruptly withdrawn. At higher doses (80 mg and above), suppression of withdrawal can increase to 48 to 72 hours in most individuals.

Repeated oral administration of LAAM can produce sufficient tolerance to block the effects of parenterally administered opiates. Chronic oral administration of 70 to 100 mg of LAAM three times weekly produces tolerance which blocks the "high" of a 25 mg dose of intravenously administered heroin for up to 72 hours; maintenance on lower doses (50 mg) of LAAM produces only partial blockage for the same period.

PHARMACOKINETICS

Absorption

LAAM is rapidly absorbed from an oral solution. Plasma levels are detectable within 15 to 30 minutes after ingestion and reach their peak within 1.5 to 2 hours at steady-state. LAAM undergoes first-pass metabolism to its demethylated metabolite nor-LAAM, which is sequentially N-demethylated to dinor-LAAM. Both metabolites are active and contribute to the extent and duration of ORLAAM's clinical activity (see PHARMACODYNAMICS).

Pharmacokinetic Model

The steady-state pharmacokinetics of LAAM were modeled from a study in 25 healthy adult addicts using three-times-a-week dosing over a 15-day observation period. LAAM and its metabolites were found to follow a multi-compartment model with extensive tissue distribution (Vd ~ 20 L/kg). LAAM had a clearance of about 0.22 L/kg/hr, mostly by conversion to nor-LAAM. Kinetic studies of the pure metabolites in man have not yet provided accurate estimates of their clearance in the absence of the precursor, but the half-lives observed in this study were 2.6 days for LAAM, approximately 2 days for nor-LAAM, and approximately 4 days for dinor-LAAM.

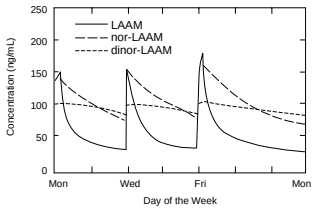
The pharmacokinetic model used to estimate steady-state plasma levels for each subject in this study assumed a common 3 mg/kg/wk dosage regimen (0.94 mg/kg on Mon. and Wed., 1.125 mg/kg on Fri.). The estimates (which fit the observed data with a correlation of better than 0.95) revealed a large inter-patient variability. There was at least a 5-fold range in peak plasma concentrations for LAAM and its metabolites across the 25 subjects over the 72-hour interval from Friday to Monday on a 3-times-a-week dosage regimen. Table 1 contains these estimates of peak and trough plasma concentrations of LAAM, nor-LAAM, and dinor-LAAM.

Table 1: Peak and Trough Estimated Steady-State Plasma Concentrations During the 72 Hour Interval (Friday to Monday) for a 65-kg Patient Given 3 mg/kg/Week on Mon./Wed./Fri.

	LAAM Mean (CV)	Nor-LAAM Mean (CV)	Dinor-LAAM Mean (CV)
Cmax(ng/mL)*	204 (34%)	173 (34%)	114 (28%)
Cmin(ng/mL)**	36 (62%)	85 (58%)	96 (34%)

*Following Friday Morning Dose
**Prior to Monday Morning Dose

Figure 1: Simulated Steady-State Plasma Concentrations of LAAM, Nor-LAAM and Dinor-LAAM following Thrice Weekly Dosing with ORLAAM



Metabolism and Elimination

The cyctochrome P450 isoform, CYP3A4, plays a major role in the metabolism of LAAM. As noted above, the formation of nor-LAAM and dinor-LAAM is by sequential demethylation, such that dinor-LAAM is formed from nor-LAAM, not directly from LAAM. While N-demethylation is the primary route of metabolism, minor pathways of elimination include direct excretion and deacetylation to methadol, nor-methadol, and dinor-methadol.

Special Populations

Gender **-** An analysis of the data from the above study showed some difference in the plasma clearance of LAAM in 8 females versus 17 males. Males showed a trend toward a slower conversion of LAAM to nor-LAAM, which may alter the plasma concentration profile of LAAM and its active opioid metabolites. Although this effect was much smaller than the observed inter-individual differences, physicians should be alert to a possible gender difference (see INDIVIDUALIZATION OF DOSAGE).

Hepatic and Renal Disease **-** At the present time no pharmacokinetics studies have been carried out in subjects with clinically significant hepatic insufficiency or serious renal impairment. Since both the pharmacokinetics and pharmacodynamics of opiate agonists may be altered in these subjects, and any additional risks of ORLAAM therapy are not well understood in such patients, physicians may choose to manage such patients with methadone due to its simpler metabolic profile.

CLINICAL TRIALS

ORLAAM has been studied in 2666 street addicts and 3319 methadone maintenance patients, including 5697 males and 288 females. During the course of 27 studies, 4610 patients received orally administered ORLAAM for up to three years in thrice-weekly doses ranging from 10 to 140 mg. Twenty-one studies provide the primary evidence upon which the dosing recommendations for ORLAAM are based.

The vast majority of patients who received ORLAAM were treated on a thrice-weekly basis, typically on Mondays, Wednesdays and Fridays (Mon./Wed./Fri.), although every-other-day dosing schedules were used in some settings. Most of the sites dosing patients with LAAM on a 3-times-a-week (Mon./Wed./Fri. or Tues./Thurs./Sat.) schedule increased the dose prior to the 72-hour inter-dose interval by 20 to 40% to obtain coverage for the full 72 hours.

In controlled clinical trials, treatment with ORLAAM was found to be comparable to treatment with methadone with respect to reduction in use of illicit opioids. ORLAAM doses in the range of 60 to 100 mg 3-times-a-week reduced the average frequency of urine samples positive for opiates to 15-20%, as did therapy with 50 to 100 mg a day of methadone. There was a trend for more patients to drop out of ORLAAM therapy than methadone therapy in the first 4 weeks of treatment (16% dropouts for ORLAAM v. 12% for methadone), but the dropout rates for both treatments rapidly declined and both were in the range of 1 to 2% per week for the remaining patients by the third month of the studies. Global ratings of patient acceptability and response to treatment were similar for both LAAM and methadone.

In the Phase III studies, ORLAAM tended to be more effective in patients perceived by staff to benefit from a reduced frequency of clinic visits and less effective in patients perceived as needing the added support of daily clinic visits.

Four independent studies were concerned with other research objectives, including induction regimens, methadone-to-ORLAAM (and ORLAAM-to-methadone) crossover ratios, and detoxification. This research involved 800 adults (including 11 females), approximately 440 of whom were methadone maintenance patients. The results of these studies, as well as the results of a nationwide Phase III usage study of 623 patients (including 204 females) in 25 representative clinics across the country, are reflected in the dosing recommendations.

INDIVIDUALIZATION OF DOSAGE

ORLAAM is intended for use as part of a comprehensive treatment plan for narcotic dependence of the opioid type. Supplying narcotic drugs to narcotic addicts for the treatment of addiction without appropriate medical evaluation, treatment planning, and counseling has not been shown to be effective, and is a violation of the law except in special circumstances.

The therapeutic goal early in treatment with ORLAAM is to reduce illicit opioid use. The dose of ORLAAM should be chosen and adjusted as needed to provide a dose that is high enough to suppress drug withdrawal, illicit drug seeking and usage, and related high-risk behavior. If opioid side effects persist once illicit drug use is controlled, the dose of ORLAAM may require further adjustment later in treatment to minimize adverse effects.

Physicians should be alert to patient differences in levels of opioid tolerance and inter-patient variability in the absorption, distribution and metabolism of both ORLAAM and its metabolites. As with methadone, an important contribution to continued abuse of illicit drugs is an inadequate dose of the treatment medication.

Initial dosage adjustment with ORLAAM is complex due to its delayed onset of action. If the starting dose is too high or if the dose is escalated too rapidly for the patient's level of tolerance, symptoms characteristic of excessive opioid effect may occur, i.e., poor concentration, sedation, and orthostatic hypotension. Patients should be watched for such symptoms, and the dose should be lowered if they appear. In rare instances, serious symptoms of narcotic overdosage may occur, leading to profound CNS and respiratory depression.

ORLAAM and its metabolites quickly accumulate to toxic levels if the doses intended for 3-times-a-week dosing are given too frequently.

The recommended doses are intended for every-other-day or 3-times-a-week dosing and **should not be given daily.**

The recommended initial dose for patients with low or unknown tolerance to opioids is 20 to 40 mg **three-times-a-week** or **every-other-day.** Successive doses may be increased by 5 to 10 mg. At least two weeks are needed to achieve a clinical plateau after a dosage adjustment. Adjustment to a dosing schedule is dependent upon the rate at which an individual develops tolerance to the increasing level of ORLAAM (and its metabolites) as well as the time required for ORLAAM and its metabolites to accumulate to steady-state levels.

The goal of dosage titration is to suppress narcotic withdrawal while avoiding excessive opioid effects due to the build-up of long-acting metabolites. It may be safer to provide extra counseling and support rather than to attempt to completely suppress a patient's withdrawal or narcotic hunger during the first week or two of therapy. On the other hand, there is the ever-present danger that patients who receive subtherapeutic starting doses will supplement with street drugs, resulting in overdose. Patients should be strongly warned against this practice. Later in the titration process, dosage adjustments are better made on a weekly basis whenever possible.

For patients on methadone maintenance whose level of tolerance is known, the recommended initial dose of ORLAAM is 1.2 to 1.3 times the patient's daily dose of methadone, not to exceed 120 mg. Care should be taken not to adjust the dose too frequently thereafter (usually 5 to 10 mg changes every second or third dose) since increasing the dose too rapidly may result in oversedation.

One major advantage of ORLAAM therapy is reduction in need for daily clinic visits and for take-home medication. In some patients, ORLAAM may not provide adequate suppression of withdrawal for a full 72 hours. For such individuals, several therapeutic options are available: (1) extra support and an explanation of reasons for the effect, (2) increasing the dose given prior to the 72-hour interval, (3) switching to an every-other-day dosing schedule, (4) dispensing a supplemental methadone dose.

Most patients do not experience withdrawal during the 72-hour inter-dose interval after reaching pharmacological steady-state **with or without** adjustment of the Friday dose. If additional opioids are required, and the patient is not eligible or appropriate for take home doses of ORLAAM, small doses of supplemental methadone should be given rather than giving ORLAAM on two consecutive days. Take-home doses of ORLAAM and methadone always pose a risk in this setting and physicians should carefully weigh the potential therapeutic benefit against the risk of diversion (see DOSAGE AND ADMINISTRATION).

Patients should receive extra support and counseling and be warned against supplementing with street drugs as they make the switch from methadone to ORLAAM. The variability in the clearance of LAAM, nor-LAAM, and dinor-LAAM and clinical experience suggest that there will be a small number of patients who require either lower or higher doses than those recommended.

DURATION OF ORLAAM THERAPY

There is no information from controlled clinical trials as to the appropriate duration of ORLAAM therapy. There are reports from investigators that some patients on ORLAAM may experience less variation in opioid effects and have less drug craving than with methadone, so ORLAAM should be considered for patients who need long-term maintenance during social and vocational rehabilitation.

When a patient has eliminated illicit drug use, achieved social and occupational stability, and made lifestyle changes to reduce the risk of relapse, consideration may be given to discontinuation of ORLAAM therapy. Such a decision should be carefully considered as part of an individualized treatment plan. Stable long-term ORLAAM therapy is preferable to repeated cycles of premature discontinuation of medication followed by relapse to uncontrolled addiction.

A patient is most likely to remain abstinent if discontinuation of medication is attempted after the achievement of behavioral objectives and is accompanied by appropriate non-pharmacological support. The rate of dose reduction should vary according to patient's response. Discontinuation of ORLAAM therapy for administrative reasons or because of adverse reactions to the drug should be managed as described below under DOSAGE AND ADMINISTRATION.

INDICATIONS

ORLAAM is indicated for the management of opiate dependence. ORLAAM should be reserved for the use in treatment of opiate-addicted patients who fail to show an acceptable response to other adequate treatments for opiate addiction, either because of insufficient effectiveness or the inability to achieve effective dose due to intolerable adverse effects from those drugs (see Black Box Warning).

CONTRAINDICATIONS

ORLAAM is contraindicated in patients with known or suspected QT prolongation (QTc interval greater than 430 [male] or 450 [female] ms). This would include patients with congenital long QT syndrome, or conditions which may lead to QT prolongation (see WARNINGS, Effects on Cardiac Conduction) such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinically significant cardiac disease, 3) treatment with Class I and Class III anti-arrhythmics, 4) treatment with monoamine oxidase inhibitors (MAOI's), 5) concomitant treatment with other drug products known to prolong the QT interval (see PRECAUTIONS, Drug Interactions), and 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia.

ORLAAM is contraindicated in patients with known hypersensitivity to LAAM.

ORLAAM is not recommended for any use other than for the treatment of opioid dependence (see WARNINGS).

WARNINGS

Administration of ORLAAM on a daily basis has led to excessive drug accumulation and risk of fatal overdose.

ORLAAM has only been studied on a thrice-weekly or every-other-day dosing regimen.

Any decision to administer ORLAAM more frequently than every other day for any reason should be approached with extreme caution. Even then only very small doses (5 to 10 mg) should be considered.

Risk of Overdose

Analysis of some of the deaths from overdose observed in the development of ORLAAM has shown that when ORLAAM is diverted into channels of abuse, the uninformed addict can become impatient with the slow onset of ORLAAM (2 to 4 hours) and take illicit drugs, resulting in a potentially lethal combined overdose when the peak ORLAAM effect develops. Due to these risks of diversion and accidental death, ORLAAM has been approved for use only when **dispensed** by a licensed facility.

Effects on Cardiac Conduction

ORLAAM has been shown to prolong the ST segment of the electrocardiogram in beagle dogs dosed five days a week, and to inhibit the rapidly-activating delayed rectifier current I_{Kr} in isolated myocytes *in vitro.* Serial EKGs performed in a human pharmacokinetics study showed a prolongation of the QTc interval in some patients which was not associated with dose.

Cases of QT prolongation and severe arrhythmias (torsade de pointes) have been observed during post-marketing treatment with ORLAAM. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of ORLAAM to determine if a prolonged QT interval (QTc greater than 430 [male] or 450 [female] ms) is present. If there is a prolonged QT interval, ORLAAM should NOT be administered. For patients in whom the potential benefit of ORLAAM treatment is felt to outweigh the risks of potentially severe arrhythmias, an ECG should be performed prior to treatment and 12-14 days after initiating treatment, and periodically thereafter to rule out any alterations in the QT interval.

ORLAAM should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, or hypomagnesemia).

ORLAAM is metabolized to active metabolites by the cytochrome P450 isoform, CYP3A4. Therefore the addition of drugs that induce this enzyme (such as rifampin, phenobarbital, and phenytoin) or inhibit this enzyme (such as ketoconazole, erythromycin, and saquinavir) could increase the levels of parent drug or its active metabolites in a patient that was previously at steady-state, and this could potentially precipitate severe arrhythmias, including torsade de pointes (see PRECAUTIONS, Drug Interactions).

Use of Narcotic Antagonists

In an individual receiving ORLAAM, the administration of the usual dose of a narcotic antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome depends on the dose of the antagonist administered and the patient's level of physical dependence. Narcotic antagonists should be used in patients receiving ORLAAM only if needed. If a narcotic antagonist is used to treat respiratory depression in the physically dependent patient, it should be administered with care and titration should begin with much smaller-than-usual doses (0.1 to 0.2 mg recommended). If the desired effect is not achieved, escalating doses may be administered every 2 to 3 minutes. If a cumulative dose of 10 mg of naloxone has been given without effect, further administration is unlikely to be of benefit (see OVERDOSAGE).

If the patient does respond to narcotic antagonists, physicians should remember that naloxone has a much shorter duration of action than ORLAAM. Such patients should remain under prolonged observation rather than being allowed to leave emergency treatment, since ORLAAM's action will outlast naloxone-induced reversal, putting the unsupervised patient at risk of relapse, a return of respiratory depression and possible death if continuing medical attention is not available. Use of other parenteral opioid antagonists may be appropriate in some cases, but only if the dosage of such drugs can be readily titrated. Oral naltrexone would not be appropriate for the treatment of ORLAAM overdose, as it has been associated with the precipitation of prolonged opioid withdrawal symptoms when used in overdose settings.

Warnings to Patients

Patients must be warned that the peak activity of ORLAAM is not immediate, and that use or abuse of other psychoactive drugs, including alcohol, may result in **fatal** overdose, especially with the first few doses of ORLAAM, either during initiation of treatment or after a lapse in treatment.

Cases of QT prolongation and serious arrhythmia (torsade de pointes) have been observed during post-marketing treatment with ORLAAM. If a patient taking ORLAAM experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures), that patient should seek medical attention immediately.

Use in High Risk Patients

Suicide attempts with opiates, especially in combination with tricyclic antidepressants, alcohol, and other CNS active agents, are part of the clinical pattern of addiction. Although outpatient therapy with ORLAAM and other drugs of this class is usually associated with a reduction in the risk of suicide, such risk is not eliminated. Individualized evaluation and treatment planning, including hospitalization, should be considered for patients who continue to exhibit uncontrolled drug use and persistent high-risk behavior despite adequate pharmacotherapy.

PRECAUTIONS

Initial Administration and Dosage Adjustment

Due to the long half-lives of ORLAAM and its metabolites, patients will not feel the full effects of the medication for at least several days. Consequently, extra care is needed when starting patients on ORLAAM and when making initial dosage adjustments (see INDIVIDUALIZATION OF DOSAGE and DOSAGE AND ADMINISTRATION).

Use in Ambulatory Patients

Initiation of therapy or excessive doses of ORLAAM may impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as driving a car or operating machinery. Patients should be warned not to engage in such activities if their alertness and behavior are affected. Most patients show no detectable impairment of ordinary tasks on ORLAAM therapy.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may make it difficult to evaluate the clinical course of patients with head injuries. In view of LAAM's profile as a mu agonist, it should be used with extreme caution and only if deemed essential in such patients.

Asthma and Other Respiratory Conditions

ORLAAM, as with other opioids, should be used with caution in patients with asthma, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnea. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Special Risk Patients

Opioids should be given with caution and at reduced initial dose in certain patients, such as the elderly or debilitated and those with significant hepatic or renal dysfunction, hypothyroidism, Addison's Disease, prostatic hypertrophy, or urethral stricture.

Acute Abdominal Conditions

As with other mu agonists, treatment with ORLAAM may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Drug Interactions

No interaction studies have been performed in humans. ORLAAM is metabolized by the cytochrome P450 isoform, CYP3A4. The addition of drugs that induce this enzyme could increase the levels of active metabolites in a patient that was previously at steady-state.

Potentially Arrhythmogenic Agents **-** Any drug known to have the potential to prolong the QT interval should not be used together with ORLAAM. Possible pharmacodynamic interactions can occur between ORLAAM and potentially arrhythmogenic agents such as class I or III antiarrhythmics, antihistamines that prolong the QT interval, antimalarials, calcium channel blockers, neuroleptics that prolong the QT interval, and antidepressants

Caution should be used when prescribing concomitant drugs known to induce hypokalemia or hypomagnesemia as they may precipitate QT prolongation and interact with ORLAAM. These would include diuretics, laxatives and supraphysiological use of steroid hormones with mineralocorticoid potential.

Polydrug and Alcohol Abusers **-** Patients who are known to abuse sedatives, tranquilizers, propoxyphene, antidepressants, benzodiazepines, and alcohol should be warned of the risk of serious overdose if these substances are taken while on ORLAAM maintenance.

Interaction with Narcotic Antagonists, Mixed Agonists/Antagonists, Partial Agonists, and Pure Agonists **-** As with other mu agonists, patients maintained on ORLAAM may experience withdrawal symptoms when administered pure narcotic antagonists, such as naloxone, naltrexone, and nalmefene, or when administered mixed agonists/antagonists or partial agonists such as pentazocine, nalbuphine, butorphanol, and buprenorphine.

In addition, agonists such as meperidine and propoxyphene, which are N-demethylated to long-acting, excitatory metabolites, should not be used by patients taking ORLAAM because they would be ineffective unless given in such high doses that the risk of toxic effects of the metabolites becomes unacceptable.

Anesthesia and Analgesia **-** Patients receiving ORLAAM will develop a similar level of tolerance for opioids as patients receiving methadone. Anesthetists and other practitioners should be prepared to adjust their management of these patients accordingly.

Other Drug Interactions **-** The anti-tuberculosis drug rifampin has been found to produce a marked (50%) reduction in serum methadone levels, leading to the appearance of symptoms of withdrawal in well-stabilized methadone maintenance patients. Similar effects on serum methadone levels have been observed for carbamazepine, phenobarbital, and phenytoin. The presumed mechanism for this effect is the induction of methadone metabolizing enzymes. Since ORLAAM is metabolized into a **more** active metabolite, nor-LAAM, administration of these drugs may **increase** ORLAAM's peak activity and/or **shorten** its duration of action.

Conversely, drugs like erythromycin, cimetidine, and anti-fungal drugs like ketoconazole that inhibit hepatic metabolism, may **slow** the onset, **lower** the activity, and/or **increase** the duration of action of ORLAAM. Caution and close observation of patients receiving these drugs are advised to allow early detection of any need to adjust the dose or dosing interval.

Information for Patients

Patients should be provided the patient package insert for ORLAAM if they are new to the drug, and in addition should be advised that:

ORLAAM, unlike methadone, is not to be taken daily, and daily use of the usual doses will lead to serious overdose.

If a patient taking ORLAAM experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures), that patient should seek medical attention immediately.

ORLAAM is slow acting and patients should be alerted to the risk of abusing any psychoactive drug, including alcohol, while on ORLAAM therapy. This is particularly important during the first 7 to 10 days of treatment, before ORLAAM has had time to exert its full pharmacologic effect.

In addition to being warned of the delay in onset of ORLAAM, patients who are transferring from ORLAAM to methadone should be informed that they should wait 48 hours after the last dose of ORLAAM before ingesting their first dose of methadone or other narcotic (see DOSAGE AND ADMINISTRATION).

Patients should inform their adult family members that, in the event of overdose, the treating physician or emergency room staff should be told that the patient is being treated with ORLAAM, a long-acting opioid which is likely to outlast naloxone-induced reversal and which requires prolonged observation and careful monitoring. In addition, the treating physician or emergency room staff should be informed that the patient is physically dependent on narcotics and that naloxone should be administered with care so as to minimize any precipitated abstinence syndrome.

As with most mu agonists, ORLAAM may interact with other CNS depressants and should be used with caution, and in reduced dosage, in patients concurrently receiving other narcotic analgesics, antihistamines, benzodiazepines, phenothiazines or other major tranquilizers, anxiolytics, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants, including alcohol. Patients should be warned of the importance of reporting the use of any of these compounds to their physicians, as serious side effects could result, including respiratory depression, hypotension, profound sedation or coma.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year carcinogenicity studies with LAAM in rats at 13 mg/kg (77 mg/m^2) and in mice at 30 mg/kg (90 mg/m^2) given orally in the diet did not show carcinogenic changes. LAAM is not mutagenic in the Ames test, the unscheduled DNA synthesis and repair test, mouse lymphoma cells in vitro, or chromosomal aberration tests in rats in vivo. LAAM tested positive in the forward mutation assay in N. crassa at 150 μg/mL in vitro and in the heritable translocation assay in mice at 21 mg/kg (63 mg/m^2). The clinical significance of these findings is not known.

Chronic treatment with LAAM at 80 mg three times a week did not produce chromosomal aberrations in peripheral human lymphocytes. Effects of LAAM on fertility in animals has not been fully evaluated.

Use in Pregnancy: Pregnancy Category C

Animal reproduction studies are not complete and there are no clinical data on the safety of ORLAAM in pregnancy. For these reasons, ORLAAM is not recommended for use in pregnancy. Women who may become pregnant should be advised of the risks of ORLAAM therapy and of the desirability of discontinuing ORLAAM prior to a planned pregnancy.

If a female patient becomes pregnant on ORLAAM despite these precautions, it is recommended she be transferred to methadone for the remainder of the pregnancy (see TRANSFER FROM ORLAAM TO METHADONE, in DOSAGE AND ADMINISTRATION). If it appears wiser to continue a specific patient on ORLAAM, the physician should be alert to possible respiratory depression of the newborn and other perinatal complications (see Labor and Delivery).

Labor and Delivery

The effects of ORLAAM on labor and delivery are not known. Like other mu agonist opioids, however, ORLAAM is expected to produce respiratory depression and a possible neonatal dependence syndrome with a delayed emergence of withdrawal symptoms. Use of ORLAAM in labor and delivery is not recommended unless, in the opinion of the treating physician, the potential benefits outweigh the possible hazards.

Nursing Mothers

The effects of LAAM on infants of nursing mothers have not been studied. It is not known if LAAM is excreted in human milk in sufficient concentration to affect an infant. Use of ORLAAM in nursing mothers is not recommended unless, in the opinion of the treating physician, the potential benefits outweigh the possible hazards.

Pediatric Use

The use of ORLAAM in addicts under 18 years of age has not been studied. Its use is not recommended.

ADVERSE REACTIONS

Physicians should be alert to palpitations, syncope, or other symptoms suggestive of episodes of irregular cardiac rhythm in patients taking ORLAAM and promptly evaluate such cases (see WARNINGS, Effects on Cardiac Conduction).

Heroin or Methadone Withdrawal Reactions

Patients presenting for ORLAAM treatment are frequently in with-

drawal from heroin or other opiates. They may display typical withdrawal symptoms which should be differentiated from ORLAAM's side effects. Patients may exhibit some or all of the following signs and symptoms associated with withdrawal from opiates: lacrimation, rhinorrhea, sneezing, yawning, perspiration, gooseflesh, fever, chilliness alternating with flushing, restlessness, irritability, insomnia, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, anorexia, nausea, vomiting, diarrhea, and weight loss. Control of such symptoms is a primary goal of therapy. However, because of the slow onset and long half-lives of ORLAAM, nor-LAAM and dinor-LAAM, overly aggressive increases in dosage to control these withdrawal symptoms with ORLAAM may result in overdose (see INDIVIDUALIZATION OF DOSAGE).

Signs and Symptoms of ORLAAM Excess

The interaction between the development and maintenance of opioid tolerance and ORLAAM dose can be complex. Dose reduction is recommended in cases where patients develop signs and symptoms of excessive ORLAAM effect, characterized by complaints of "feeling wired", poor concentration, drowsiness, and possibly dizziness on standing.

ORLAAM Withdrawal

Patients may experience withdrawal symptoms (nasal congestion, abdominal symptoms, diarrhea, muscle aches, anxiety) over the 72-hour dosing interval if the dose of ORLAAM is too low. This may be managed as described under INDIVIDUALIZATION OF DOSAGE, but physicians should be alert to the possible need for dose or dose schedule adjustments if patients complain of weekend withdrawal symptoms in the last day of the 72-hour dosing interval.

Adverse Reactions on Stable Therapy

The following adverse events were observed in the 25-site, 623-patient usage study in male and female opiate addicts (see CLINICAL TRIALS). These signs and symptoms were reported during the second and third months of treatment with ORLAAM, and were considered severe enough to require medical evaluation. In this study, both questionnaires and spontaneous reports were used to gather information. Questionnaire-elicited symptom frequencies were about five times as frequent as the spontaneous reporting frequencies given below.

Incidence greater than 1%, Probably Causally Related

Body as a Whole -	Asthenia*, back pain, chills, edema, hot flashes (males 2:1), flu syndrome and malaise (11%).
Gastrointestinal -	Abdominal pain*, constipation*, diarrhea, dry mouth, nausea and vomiting.
Musculoskeletal -	Arthralgia*
Nervous System -	Abnormal dreams, anxiety, decreased sex drive, depression, euphoria, headache, hypesthesia, insomnia (9.1%), nervousness*, somnolence.
Respiratory -	Cough, rhinitis, and yawning.
Skin/appendages -	Rash, sweating*.
Special Senses -	Blurred vision.
Urogenital -	Difficult ejaculation*, impotence*.

*Reactions in 3-9% of patients; reactions in 1-3% are unmarked.

Incidence less than 1%, Probably Causally Related

Cardiovascular -	Postural hypotension.
Musculoskeletal -	Myalgia.
Special Senses -	Tearing.

Causal Relationship Unknown

These reactions were reported with low frequency in controlled and uncontrolled studies of LAAM, are not known to be causally related to the administration of the drug, and are provided as alerting information for physicians.

Cardiovascular -	Hypertension
Hepatic -	Hepatitis and abnormal liver function tests.
Urogenital -	Amenorrhea, pyuria.

The following adverse reactions have been reported in the post-marketing setting (all reactions in less than 1% of patients).

Body as a Whole -	Altered hormone level, chest pain.
Cardiovascular -	QT interval prolongation, torsade de pointes, cardiac arrest, ST segment elevation, ventricular tachycardia, myocardial infarction, angina pectoris, syncope, migraine.
Nervous System -	Convulsions, confusion, hallucination, incoordination, amnesia.
Respiratory -	Apnea, dyspnea.
Urogenital -	Breast enlargement.

DRUG DEPENDENCE

ORLAAM is a Schedule II controlled substance under the Federal Controlled Substances Act. ORLAAM produces dependence of the morphine-type and has potential for abuse. Tolerance and physical dependence will develop upon repeated administration. As with methadone and any other narcotic administered to narcotic addicts, ORLAAM is at risk for diversion and illicit use, and should be handled accordingly (see WARNINGS).

OVERDOSE

Signs and Symptoms

All but a few cases of ORLAAM overdose have involved multiple drugs. Overdose on ORLAAM alone is rare and has always been the result of too frequent (daily) dosing. Overdose is primarily of concern in persons not tolerant to opiates, since in such individuals a dose of 20 to 40 mg of ORLAAM may cause somnolence, and a larger initial dose may cause serious overdose. Tolerant individuals will generally not show symptoms unless higher doses are administered.

In ORLAAM overdose, as with other mu agonist opioids, the following signs and symptoms should be anticipated: respiratory depression (decrease in respiratory rate and/or tidal volume, Cheyenne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, bradycardia, and hypotension. In severe overdose, apnea, circulatory collapse, pulmonary edema, cardiac arrest and death may occur.

Treatment

In the case of ORLAAM overdose, protect the patient's airway and support ventilation and circulation. Absorption of ORLAAM from the gastrointestinal tract may be decreased by gastric emptying and/or administration of activated charcoal. (Safeguard the patient's airway when employing gastric emptying or administering charcoal in any patient with diminished consciousness). Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion are unlikely to be beneficial for ORLAAM overdose due to its high lipid solubility and large volume of distribution.

In managing ORLAAM overdose, the physician should consider the possibility of multiple drugs, the interaction between drugs, and any unusual drug kinetics in the patient. Naloxone may be given to antagonize opiate effects, but the airway must be secured as vomiting may ensue. If possible, naloxone should be titrated to clinical effect rather than given as a large single bolus, since rapid reversal of opioid effects by large naloxone doses can cause severe precipitated withdrawal effects that may include cardiac instability. If a patient has received a total of 10 mg of naloxone without clinical response, the diagnosis of opioid overdose is unlikely.

If the patient does respond to naloxone, the physician should remember that the duration of ORLAAM activity is much longer (days) than that of naloxone (minutes) and repeated dosing with or continuous intravenous infusion of naloxone is likely to be required. Use of oral naltrexone in this setting is not recommended because it may precipitate prolonged opioid withdrawal symptoms (see Use of Narcotic Antagonists).

DOSAGE AND ADMINISTRATION

ORLAAM produces opioid effects and a high degree of opioid tolerance that inhibits drug-seeking behavior and blocks the euphoria produced by the usual doses of heroin. The dose of ORLAAM in each patient should be adjusted to achieve the optimal therapeutic benefit with acceptable adverse opioid effects (see INDIVIDUALIZATION OF DOSAGE).

ORLAAM must always be diluted before administration, and should be mixed with diluent prior to dispensing. To avoid confusion between prepared doses of ORLAAM and methadone, the liquid used to dilute ORLAAM should be a different color from that used to dilute methadone in any specific clinic setting.

ORLAAM DOSING

Dosing Schedules

ORLAAM is usually administered three times a week, either on Monday, Wednesday and Friday, or on Tuesday, Thursday and Saturday. If withdrawal is a problem during the 72-hour inter-dose interval, the preceding dose may be increased. In some cases, an every-other-day schedule may be appropriate (see INDIVIDUALIZATION OF DOSAGE).

The usual doses of ORLAAM must not be given on consecutive days because of the risk of fatal overdose. No dose mentioned in this label is **ever** meant to be given as a daily dose (see WARNINGS).

INDUCTION

The initial dose of ORLAAM for street addicts should be 20 to 40 mg. Each subsequent dose, administered at 48- or 72-hour intervals, may be adjusted in increments of 5 to 10 mg until a pharmacokinetic and pharmacodynamic steady-state is reached, usually within 1 or 2 weeks (see INDIVIDUALIZATION OF DOSAGE).

Patients dependent on methadone may require higher initial doses of ORLAAM. The suggested initial 3-times-a-week dose of ORLAAM for such patients is 1.2 to 1.3 times the daily methadone maintenance dose being replaced. This initial dose should not exceed 120 mg and subsequent doses, administered at 48- or 72-hour intervals, should be adjusted according to clinical response.

Most patients can tolerate the 72-hour inter-dose interval during the induction period. Some patients may require additional intervention (see INDIVIDUALIZATION OF DOSAGE). If additional opioids are required, and the patient is not eligible or appropriate for take home doses of ORLAAM, supplemental methadone in small doses should be given rather than giving ORLAAM on two consecutive days. Take-home doses of ORLAAM and methadone always pose a risk in this setting and physicians should carefully weigh the potential therapeutic benefit against the risk of diversion.

In some cases, where the degree of tolerance is unknown, patients can be started on methadone to facilitate more rapid titration to an effective dose, then converted to ORLAAM after a few weeks of methadone therapy.

The crossover from methadone to ORLAAM should be accomplished in a single dose; complete transfer to ORLAAM is simpler and preferable to more complex regimens involving escalating doses of

ORLAAM and decreasing doses of methadone.

Dosage should be carefully titrated to the individual; induction too rapid for the patient's level of tolerance may result in overdose. Serious hazards, as seen in association with all narcotic analgesics, are respiratory depression and, to a lesser extent, circulatory depression.

MAINTENANCE

Most patients will be stabilized on doses in the range of 60 to 90 mg, 3-times-a-week. Doses as low as 10 mg and as high as 140 mg three times a week have been given in clinical studies.

Supplemental dosing over the 72-hour inter-dose interval (weekend) is rarely needed. For example, if a patient on a Mon./Wed./Fri. schedule complains of withdrawal on Sundays, the recommended dosage adjustment is to increase the Friday dose in 5 to 10 mg increments up to 40% over the Mon./Wed. dose or to a maximum of 140 mg.

Most patients do not experience withdrawal during the 72-hour inter-dose interval after reaching pharmacological steady-state **with or without** adjustment of the Friday dose. If additional opioids are required, and the patient is not eligible or appropriate for take home doses of ORLAAM, small doses of supplemental methadone should be given rather than giving ORLAAM on two consecutive days. Take-home doses of ORLAAM and methadone always pose a risk in this setting and physicians should carefully weigh the potential therapeutic benefit against the risk of diversion (see DOSAGE AND ADMINISTRATION).

If withdrawal symptoms persist after adjustment of dose, consideration may be given to every-other-day dosing if clinic hours permit. If the clinic is not open seven days a week and every-other day dosing is not practical, the patient's schedule may be adjusted so the 72-hour interval occurs during the week and the patient can come to the clinic to receive a supplemental dose of methadone (see INDIVIDUALIZATION OF DOSAGE).

The maximum **total** amount of ORLAAM recommended for any patient is 140-140-140 mg or 130-130-180 mg on a thrice-weekly schedule or 140 mg every other day.

TAKE-HOME DOSES

If it is determined that a patient is responsible in handling opioid drugs then ORLAAM take-home doses are permitted. Refer to 42 CFR Part 8 for specific restrictions.

REINDUCTION AFTER AN UNPLANNED LAPSE IN DOSING

Following a lapse of <u>one</u> ORLAAM dose:

1) If a patient comes to the clinic to be dosed **on the day following a missed scheduled dose** (misses Monday, arrives Tuesday), the regular Monday dose should be administered on Tuesday, with the scheduled Wednesday dose administered on Thursday and the Friday dose given on Saturday. The patient's regular schedule may be resumed the following Monday (misses Wednesday, receives the regular dose on Thursday and Saturday, and returns to the regular Monday/Wednesday/Friday dosing schedule the next week).
2) If a patient misses one dose and comes to the clinic **on the day of the next scheduled dose** (misses Monday, arrives Wednesday), the usual dose will be well tolerated in most instances, although a reduced dose may be appropriate in selected cases.

Following a lapse of <u>more than one</u> ORLAAM dose:

Patients should be reinducted at an initial dose of 1/2 or 3/4 their previous ORLAAM dose, followed by increases of 5 to 10 mg every dosing day (48- or 72-hours intervals) until their previous maintenance dose is achieved. Patients who have been off of ORLAAM treatment for more than a week should be reinducted.

TRANSFER FROM ORLAAM TO METHADONE

Patients maintained on ORLAAM may be transferred directly to methadone. Because of the difference between the two compounds' metabolites and their pharmacological half-lives, it is recommended that methadone be started on a daily dose at 80% of the ORLAAM dose being replaced; the initial methadone dose must be given no sooner than 48 hours after the last ORLAAM dose. Subsequent increases or decreases of 5 to 10 mg in the daily methadone dose may be given to control symptoms of withdrawal or, less likely, symptoms of excessive sedation, in accordance with clinical observations.

DETOXIFICATION FROM ORLAAM

There is a limited experience with detoxifying patients from ORLAAM in a systematic manner, and both gradual reduction (5 to 10% a week) and abrupt withdrawal schedules have been used successfully. The decision to discontinue ORLAAM therapy should be made as part of a comprehensive treatment plan (see INDIVIDUALIZATION OF DOSAGE).

SAFETY AND HANDLING

ORLAAM is a solution of a potent narcotic (LAAM). There are no known specific hazards associated with dermal and aerosol exposure to ORLAAM. In case of accidental dermal exposure, promptly remove contaminated clothing and rinse the affected skin with cool water.

Sales of ORLAAM are restricted to clinics that have received training in its use. Since ORLAAM can be potentially dangerous if diverted, appropriate security measures should be taken to safeguard stock of ORLAAM as required by 21 CFR 1301.74.

HOW SUPPLIED

ORLAAM Oral Solution (10 mg/mL) is a clear, colorless liquid supplied in plastic bottles as follows:

NDC 0054-3649-63: **500 mL per bottle**

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from direct sunlight.

ORLAAM is compatible with the materials used in most dispensing systems. Information about obtaining appropriate dispensing systems suitable for use with ORLAAM is available from the manufacturer upon request.

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Roxane Laboratories, Inc.
Columbus, Ohio 43216